

23. (Amended) An isolated nucleic acid molecule consisting of a nucleotide sequence of SEQ ID NO: 47 or the complement of SEQ ID NO: 47.

### REMARKS

#### Amendments to the Specification

Applicants have amended the specification to correct an inadvertent error in the description of the length of the spastin exon. The specification has been amended to indicate that the length of the exon is 12,793 base pairs in length. Support for this amendment is found, for example, in Figures 9A-9F. No new matter has been added. Entry of these amendments is respectfully requested.

#### Amendments to the Claims

Claims 5, 13-22 and 24-39 have been canceled, and Claims 1, 2, 6, 8 and 23 have been amended to further and more particularly define that which Applicants regard as their invention.

Support for amendments to the claims is found throughout the specification. For example, page 15, lines 2-4, describe SEQ ID NO: 7 and the deletion of a Thymine at position 6594 of SEQ ID NO: 1 (as indicated by positions 6593 and 6594 of SEQ ID NO: 7). On page 19, lines 1-15, for example, the use of fragments of, *inter alia*, SEQ ID NOS: 7 and 47, are described. The use of these fragments is described for highly stringent hybridizations and for use as probes. Such fragments can be "at least about 15 nt" in length. On page 9, lines 13-25, and page 13, lines 15-17, for example, a human gene with an intron of at least 11,487 nt is disclosed.

#### Informalities

The Examiner objects to the Specification "because it contains an embedded hyperlink and/or other form of browser-executable code (page 42, lines 22-28)" (page 2 of the Office Action).

Applicants have amended the Specification to obviate this issue. Reconsideration and withdrawal of the objection is respectfully requested.

Rejection of Claims 2-4 and 6-8 Under 35 U.S.C. §112, First Paragraph

Claims 2-4 and 6-8 are rejected under 35 U.S.C. §112, first paragraph, as “containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” (page 2 of the Office Action)

Specifically, the Examiner asserts that

Claims 2-4 and 6-8 are directed to a nucleic acid comprising an exon from a vertebrate gene wherein the exon is at [*sic*] 1150 base pairs; a portion of a nucleic acid is [*sic*] at least 10 nucleotides of SEQ ID NO: 7 or of the complement of SEQ ID NO: 7; a nucleic acid comprising a nucleotide sequence, which has at least 60% sequence identity to SEQ ID NO: 7 or a complement of SEQ ID NO: 7; and a nucleic acid which hybridizes under stringency conditions to a nucleotide sequence of SEQ ID NO: 7 or of the complement of SEQ ID NO: 7. (pages 2-3 of the Office Action)

And, further,

Without guidance on the identities of the nucleic acids having at least 60% sequence identity to SEQ ID NO:7 or of fragments of SEQ ID NO:7, one skilled in the art would not know which region of SEQ ID NO:7 is essential for coding a functional protein. (page 3 of the Office Action)

Applicants have amended Claims 2 and 6-8. Claim 4 depends on Claim 2. As amended, Claim 2 is directed to a nucleic acid molecule comprising an exon from a vertebrate gene wherein said exon is at least 12,793 base pairs in length, as is supported in the Specification (see above). Claims 4, 6 and 8 have been amended such that a particular position of SEQ ID NO: 7 (nt 6594) is indicated, thereby directing one of skill in the art to a specific region of SEQ ID NO: 7.

As amended, the subject matter claimed is described in the Specification in such a way as to convey to one of skill in the art that the inventors had possession of the claimed invention at the time of filing. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 5-12 and 23 Under 35 U.S.C. §112, Second Paragraph

Claims 1, 5-12 and 23 are rejected under 35 U.S.C. §112, second paragraph, as being “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” (page 4 of the Office Action).

The Examiner states that Claims 1, 5-12 and 23 contain non-elected sequences. Claim 5 has been cancelled, and Claims 1, 6-8 and 23 have been amended. Claims 5 and 9-12 depend on claims that have been amended. As amended, all claims are directed to sequences that were elected in Applicants’ Reply to Restriction Requirement as filed April 22, 2002.

The Examiner states that Claim 2 is indefinite for use of the term “at least,” stating that it is unclear what the upper limit for the number of base pairs is. Applicants note that Claim 2 has been amended and is directed to a nucleic acid molecule comprising an exon from a vertebrate gene wherein said exon is at least 11,487 base pairs in length. The MPEP allows for open-ended numerical ranges, although note is made that they should be examined carefully for definiteness (MPEP §2173.05(c)). However, the MPEP further suggests that claims having open-ended numerical ranges are indefinite only to the extent that they create ambiguity in light of the rest of the claim language.

[W]hen an independent claim recites a composition comprising ‘at least 20% sodium’ and a dependent claim sets forth specific amounts of nonsodium ingredients which add up to 100%, apparently to the exclusion of sodium, an ambiguity is created with regard to the ‘at least’ limitation.” (MPEP §2173.05(c)).

Neither Claim 2 nor subsequent dependent claims create such an ambiguity. Since the claims do not create an ambiguity and since open-ended numerical ranges are otherwise considered to be definite, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner states that Claim 6 is indefinite for use of the terms “at least about” and “portion.” Applicants have amended Claim 6 such that it is directed to an isolated polynucleotide fragment comprising nucleotide position 6594 of SEQ ID NO: 7, wherein the fragment is at least 15 nucleotides in length. Applicants note that the term “fragment” is clearly described throughout the Specification. For example, on page 19, lines 4-8, Applicants describe particular nucleic acid fragments useful in the invention. In light of the amendment and remarks, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner states that Claim 7 is indefinite for use of the term “at least about 60% identical to a nucleotide sequence.” Applicants have amended Claim 7, thereby obviating the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

#### Rejection of Claim 6 Under 35 U.S.C. §102(a)

Claim 6 is rejected under 35 U.S.C §102(a) as being anticipated by Nagase *et al.* (1998. *DNA Res.*, 5:277-286; Reference AT).

The Examiner states, “Nagase *et al.* disclose a Homo sapiens mRNA for KIAA070 protein..., which has 100% sequence homology to nucleotides 12200-12792 of SEQ ID NO:7.” (Page 5 of the Office Action).

Applicants have amended Claim 6 such that Claim 6 is directed to an isolated polynucleotide fragment of SEQ ID NO: 7 of at least 15 nucleotides in length comprising nucleotide positions 6593 and 6594 of SEQ ID NO: 7. The teachings of Nagase *et al.* do not anticipate Claim 6 as amended. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

#### Rejection of Claims 2 and 3 Under 35 U.S.C. §102(a)

Claims 2 and 3 are rejected under 35 U.S.C §102(a) as being anticipated by Desseyn *et al.* (1997. *J. Biol. Chem.*, 272:16873-16883; Reference AU3).

The Examiner states, “Desseyn *et al.* disclose the central exon of human mucin Gene MUC5B contains 10,713 base pairs.” (page 5 of the Office Action). Applicants have amended Claim 2 to recite an exon that is at least 12,793 base pairs in length. Claim 3 depends on Claim

2. As amended, Claims 2 and 3 are not anticipated by the teachings of Desseyn *et al.* Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 6 Under 35 U.S.C. §102(a)

Claim 6 is rejected under 35 U.S.C §102(a) as being anticipated by Bouillaud *et al.* (GenBank Accession No. R17106, updated June 12, 1996; Reference U).

The Examiner states, "Bouillaud *et al.* disclose a mRNA sequence, a Homo sapiens cDNA clone 20108, has 32.7% sequence homology to nucleotides 5300-6700 of SEQ ID NO:7, the sequence of R17106 contains the same portion of at least 10 nucleotides as SEQ ID NO:7." (page 5 of the Office Action).

Applicants have amended Claim 6 such that Claim 6 is directed to an isolated polynucleotide fragment of SEQ ID NO: 7 of at least 15 nucleotides in length comprising nucleotide positions 6593 and 6594 of SEQ ID NO: 7. Applicants direct the Examiner's attention to the alignment cited in the Office Action; specifically, Applicants direct the Examiner's attention to the sequence "atgtga" (nt 1292-1296 of the query sequence of page 2 of the Bouillaud alignment). This sequence corresponds to nt 6591-6596 of SEQ ID NO: 7. The teachings of Bouillaud *et al.* do not anticipate Claim 6 as amended. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,  
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MARKED UP VERSION OF AMENDMENTSSpecification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 2, lines 4 through 21 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

- - - As described herein, the ARSACS gene, referred to herein as “*spastin*” (also known as *sacsin*), has been mapped to chromosome 13q11 by linkage analysis and cloned from human, mouse and hamster. The gene was identified by using fine-structure linkage disequilibrium (LD) mapping to narrow the disease interval and then performing sample-sequencing to identify candidate genes. The *spastin* gene has a remarkable feature in that it contains a large exon spanning at least 12,793 [12,794] base pairs of genomic DNA and comprises an open-reading frame of 11,487 base pairs. As described herein the gene is highly conserved in mouse. This exon of *spastin* is the largest found in any vertebrate organism. The deduced protein contains three large domains with sequence similarity to each other, as well as to the protein predicted to be encoded by an open reading frame identified in *Arabidopsis* genomic DNA. These domains contain a subdomain with sequence similarity to heat-shock proteins, suggesting a role in chaperone-mediated protein folding. *Spastin* appears to be expressed in a wide variety of tissues including brain and central nervous system. Alterations in the *spastin* gene have been identified as described herein which correlate strongly with ARSACS, including at least two alterations which have severe effects on the encoded protein, providing strong evidence that mutations in the open reading frame of the *spastin* gene are responsible for ARSACS. - - -

Replace the paragraph at page 9, lines 13 through 25 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

- - - A 20 kb sequence contig revealed a huge genomic open reading frame (ORF) of 11,487 base pairs that encodes 3829 amino acids (SEQ ID NO: 2). The open reading frame (ORF) begins with an

AUG codon preceded by an in-frame stop codon 75 bp upstream and continues for a total of 3,829 codons before encountering a stop codon. One large cDNA (KIAA0730) derived from a brain library and over 30 ESTs overlap the ORF and allowed the determination of the 3' untranslated region (UTR), which extends 1,307 bp to a polyadenylation site (Figure 1). The existence of this gigantic exon was confirmed by analyzing RT-PCR products spanning the entire mRNA; this analysis showed perfect correspondence between the mRNA and genomic DNA sequence. Thus, the total length of the exon must be at least 12,793 [12,794] bp. A probe derived from within this sequence detects a transcript of approximately 12.8 kb on a Northern blot, suggesting that the identified exonic sequence may constitute an intronless gene, although the possibility of a small 5' exon cannot be excluded. - - -

Replace the paragraph at page 13, lines 8 through 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

- - - As described herein, sample-sequencing of the ARSACS critical region, in combination with directed sequencing of specific subclones and computer-aided analysis led to the characterization of a very large exon directly from genomic DNA. This likely represents the entire coding sequence of the *spastin* gene as the first methionine is preceded by an in-frame stop codon 75 bp upstream. RT-PCR demonstrated that the sequence, from this 75 bp until the polyadenylation site, is transcribed. *Spastin* appears to be an intronless gene, although a non-coding upstream exon cannot be ruled out. The *spastin* exon of at least 12,793 [12,794] bp encoding an ORF of 11,487 bp represents the largest exon and the largest ORF within an exon found in any vertebrate so far. The next largest exons reported are the X (inactive)-specific transcript (*XIST*) (11,363 bp) which does not code for a protein (13), and the large central exon of the mucin gene (*MUC5B*) which is 10,713 bp long (14). - - -

Replace the paragraph at page 42, lines 22 through 28 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

- - - Computational Analyses

World Wide Web-based hyper-text (http) sequence analysis included (using default parameters):

BLAST:[<http://www.ncbi.nlm.nih.gov/cgi-bin/BLAST/nph-nesblast?Jform=1>;

FASTA:[<http://www.ebi.ac.uk/searches/fasta.html>;

PSORT:[<http://psort.nibb.ac.jp:8800>;

EXPASY Proteomics tools:[<http://www.expasy.ch/tools/>;

BCM Search Launcher:[<http://www.hgsc.bcm.tmc.edu/SearchLauncher/>;

[[mac-search-launcher:ftp://dot.bcm.tmc.edu/pub/software/search-launcher/](http://mac-search-launcher:ftp://dot.bcm.tmc.edu/pub/software/search-launcher/)];

COILS (35) web server:[[http://www.ch.embnet.org/software/COILS\\_form.html](http://www.ch.embnet.org/software/COILS_form.html);

and the following ftp site:

[mac-search-launcher: dot.bcm.tmc.edu/pub/software/search-launcher/](http://mac-search-launcher:ftp://dot.bcm.tmc.edu/pub/software/search-launcher/).

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Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 7 or the complement of SEQ ID NO: 7 [selected from the group consisting of:
  - a) SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15; and
  - b) the complement of SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15].
2. (Amended) An isolated nucleic acid molecule comprising an exon from a vertebrate gene wherein said exon is at least 12,793 [1150] base pairs in length.
6. (Amended) An isolated polynucleotide fragment of SEQ ID NO: 7[portion of a nucleic acid sequence selected from the group consisting of:
  - a) SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15; and
  - b) the complement of SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15,]comprising nucleotide positions 6593 and 6594 of SEQ ID NO: 7, wherein the fragment[portion] is at least 15 [about 10] nucleotides in length.



7. (Amended) A nucleic acid molecule comprising a nucleotide sequence comprising [which is] at least [about] 60% sequence identity [identical] to SEQ ID NO: 7 or the complement of SEQ ID NO: 7 [a nucleotide sequence selected from the group consisting of:
- a) SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15; and
  - b) the complement of SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15].
8. (Amended) A nucleic acid molecule that[which] hybridizes under high stringency conditions to a nucleotide sequence comprising nucleotide positions 6593 and 6594 of SEQ ID NO: 7 and at least ten flanking nucleotides of SEQ ID NO: 7 [selected from the group consisting of:
- a) SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15; and
  - b) the complement of SEQ ID NOS: 1, 3, 7, 9, 11, 12, 13, 14 and 15].
23. (Amended) An isolated nucleic acid molecule consisting of a nucleotide sequence of SEQ ID NO: 47 or the complement of SEQ ID NO: 47 [selected from the group consisting of:
- a) SEQ ID NOS: 21-66; and
  - b) the complement of SEQ ID NOS: 21-66].